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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | | ATTORNEY DOCKET NO. |
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| 09/163,272 | 09/29/98 | DINSMORE | J | DNI-041 |

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| EXAMINER | |
|---|---|
| MAYO,K | |
| **ART UNIT** | **PAPER NUMBER** |
| 1633 | 6 |

**DATE MAILED:** 12/07/99

**Please find below and/or attached an Office communication concerning this application or proceeding.**

**Commissioner of Patents and Trademarks**

# Office Action Summary

| Application No. | Applicant(s) |
|---|---|
| 09/163,272 | Dinsmore |
| **Examiner** | **Group Art Unit** |
| Kris Pelham Mayo | 1633 |

☐ Responsive to communication(s) filed on _____ .

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

**Disposition of Claims**

☒ Claim(s) *1-38* is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-38* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

**Application Papers**

☒ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☒ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. § 119**

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____ .

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____ .

☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

**Attachment(s)**

☒ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☒ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

*--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---*

## DETAILED ACTION

### *Priority*

Applicant's claim for priority to Provisional Application Number 06/091,193, filed on 06/30/1998 is acknowledged. Priority has been perfected.

### *Drawings*

This application has been filed with informal drawings which are acceptable for examination purposes only. Formal drawings will be required when the application is allowed. Note the enclosed PTO Form 948 Notice of Draftsperson's Patent Drawing Review outlining the objections to the drawings in the instant application.

### *Specification*

The disclosure is objected to because of the following informalities:

Several minor typographical errors exist such as those found on: page 8, line 4 - period missing at end of sentence; page 11, lines 3 and 30 - "hypopneumonia" should read "hyopneumoniae"; page 11, line 7 - "hemophilus suis " is listed twice; and page 31, line 27 - "assesses" should read "assessed".

Appropriate correction of these and all other typographical errors is necessary.

***Claim Rejections - 35 USC § 112***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-38 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a composition for transplantation into a rat or a mouse to treat spinal cord damage selected from the group consisting of partial spinal cord transection in said rat and spinal cord degeneration associated with SOD (expresses a human Cu/Zn superoxide dismutase mutation) mice, comprising an isolated spinal cord cell obtained from a pig, such that partial integration and survival of the porcine xenographic transplant occurs, and partial synaptic connections are established as determined by behavioral testing; wherein, prior to introduction into the recipient mouse, the cell is contacted with an anti-MHC class I $F(ab')_2$ fragment of monoclonal antibody PT85, but does not activate complement or induce cell lysis; wherein the composition further comprises at least one agent or factor selected from the group consisting of brain-derived neurotrophic factor, ciliary neurotrophic factor, platelet-derived growth factor, neural growth factor, neurotrophin-3, neurotrophin 4/5, basic fibroblast growth factor, and methylprednisolone; and wherein the cell is obtained from a pig predetermined to be free from at least one organism selected from the groups consisting of zoonotic, cross-placental and neurotropic organisms; and a method of treatment of partial spinal cord transection in rats and spinal cord degeneration associated with SOD mice comprising administering said composition to

said rat or mouse, such that integration and survival of the porcine xenographic transplant occurs, and synaptic connections are established as determined by behavioral testing; and a method of treatment of spinal cord degeneration comprising amyotrophic lateral sclerosis in humans, comprising administering said composition to said human, such that integration and survival of the porcine xenographic transplant occurs, and synaptic connections are established as determined by behavioral testing, does not reasonably provide enablement for any and all xenographic subjects, any and all types of spinal cord damage or injury, any and all antigens, any and all cell surface antigen alterations, any and all treatments, any and all molecules, and any and all neurodegenerative disorders. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Claims 1-38, as written, read on any and all xenogeneic subjects. However, the specification fails to provide any teachings or guidance with regard to the generation or use of any xenogeneic subject, other than the rat, the SOD mouse, and the human. At the time the invention was made, the rat had wide acceptance in the art as an animal model for spinal cord injuries. Also at the time the invention was made, the SOD transgenic mouse model had acceptance in the art as an animal model for human ALS (amyotrophic lateral sclerosis), as the SOD mouse displays a neuropathology resembling the pathogenesis of ALS in humans. In the unpredictable arts of transplant therapy and animal models for spinal cord injury and disease, however, it is not known what effect, if any, the transplant would have on a subject of another species; if an effect were

made, it is not known whether that effect would be positive, such that treatment of spinal cord injury or degenerative disease would be achieved. In the absence of teaching or guidance in the specification, one of ordinary skill in the art would have been required to undergo undue experimentation to determine which other xenogeneic subjects could be the recipient of the porcine spinal cord cell transplant.

Claims 8-11 and 25-30, as written, read on any and all antigens. However, the specification fails to provide any teachings or guidance with regard to any type of antigen other than an MHC class I antigen. At the time the invention was made, it was known in the art that numerous antigens exist on the cell surface of a porcine spinal cord cell that would be capable of stimulating an immune response against the cell in a xenogeneic subject. Because numerous antigens exist, as explained *infra*, there would be numerous opportunities for the transplant recipient to mount an immune response against the transplanted cells, resulting in transplant rejection. In the absence of teaching or guidance in the specification on any other cell surface antigens, one of ordinary skill in the art would have been required to undergo undue experimentation to determine which other porcine spinal cord cell surface antigens would incite an immune response in the transplant recipient such that the integrity of the transplant would be in jeopardy.

Claims 1-38, as written, read on any and all types of spinal cord damage and injury. However, the specification fails to provide any teachings or guidance with regard to any type of spinal cord damage or injury, other than partial spinal cord transection. It is not known what effect, if any, the transplant would have on subjects with other types of injury, including contusions and hematomas (such as from direct blunt trauma), compressions (such as from intervertebral disk protrusion or rupture, tumors, foreign bodies, or parasites), and full-thickness transections (such as from trauma). The presence of different inflammatory mediators, cells and physical barriers (such as a complete gap between cranial and caudal spinal cord fragments), depending of the specific type of injury may interfere with the transplant such that treatment is not achieved. In the absence of teaching or guidance in the specification, one of ordinary skill in the art would have been required to undergo undue experimentation to determine which other types of spinal cord damage or injury could be treated by the claimed composition and methods of the instant application.

Claims 26-30, as written, read on any and all molecules. However, the specification fails to provide any teachings or guidance with regard to any molecule other than the $F(ab')_2$ fragment of a monoclonal antibody PT85. It is not known what effect, if any, any and all molecules would have on the antigen. For example, if a molecule of water was bound to the antigen, would it make it any less antigenic? Just as the scope of the antigen is limited by the teaching in the specification, as elucidated *supra*, the scope of the antibody which binds the antigen is also limited. In the absence of teaching or guidance in the specification on any other molecules, one of

ordinary skill in the art would have been required to undergo undue experimentation to determine which other porcine antibodies would bind to the MHC class I antigen to inhibit rejection of the cell when introduced into the subject.

Claims 8-11, as written, read on any and all antigenic alterations. However, the specification fails to provide any teachings or guidance with regard to any alterations other than being bound by the $F(ab')_2$ fragment of a monoclonal antibody PT85. At the time the invention was made, other methods of altering antigens were known in the art, including enzymatic and heat-induced inactivation. In the absence of teaching or guidance in the specification on any other methods of antigenic alteration, one of ordinary skill in the art would have been required to undergo undue experimentation to determine which other methods of antigenic alteration would result n inhibition of rejection of the porcine spinal cord cell upon introduction into the transplant recipient.

Claims 1-38, as written, read on any and all treatments of spinal cord damage. However, the specification fails to provide any teachings or guidance with regard to all treatment other than the establishment of partial integration and survival of the porcine xenographic transplant, and partial establishment of synaptic connections, as determined by behavioral testing. At the time the invention was made, it was known in the art that treatment could be anything from the integration and survival of one transplanted cell, and the establishment of one synaptic connection to the complete reconnection and restoration of all motor and sensory neurological function subsequent to full-thickness transection of the spinal cord. In the absence of teaching or guidance in the

specification on any other treatment outcomes, other than the establishment of partial integration and survival of the porcine xenographic transplant, and partial establishment of synaptic connections, as determined by behavioral testing, one of ordinary skill in the art would have been required to undergo undue experimentation to determine what other treatment outcomes were possible.

Claim 37, as written, reads on any and all neurodegenerative disorders. However, the specification fails to provide any teachings or guidance with regard to all neurodegenerative disorders other than amyotrophic lateral sclerosis. At the time the invention was made, numerous other neurodegenerative disorders were known in the art, such as Alzheimer's Disease, Parkinsonism, and Huntington's Disease. It is not known what effect, if any, administration of the composition of the claimed invention would have on any of these neurodegenerative disorders. In the absence of teaching or guidance in the specification on the treatment of any other neurodegenerative diseases, one of ordinary skill in the art would have been required to undergo undue experimentation to determine what other neurodegenerative diseases could be treated by the claimed composition and method of the instant application.

Claims 1-38 are extremely broad, encompassing any and all xenographic subjects, any and all types of spinal cord damage or injury, any and all antigens, any and all cell surface antigen alterations, any and all treatments, any and all molecules, and any and all neurodegenerative disorders. The courts have stated that reasonable correlation must exist between scope of exclusive right to patent application and scope of enablement set forth in patent application. See

27 USPQ2d 1662 *Ex parte Maizel*. Scope of Enablement is considered in view of the Wands factors (MPEP 2164.01 (a)). In view of the quantity of experimentation necessary to determine the parameters listed above, the lack of direction or guidance provided by the specification, the absence of working examples for the demonstration or correlation of any xenographic subject other than the rat or SOD mouse, of any type of spinal cord damage or injury other than partial transection or SOD mouse-associated degenerative disease, of any antigen other than the MHC class I antigen, or any molecule other than the $F(ab')_2$ fragment of monoclonal antibody PT85, of any other alteration of the cell surface antigen other than the binding by the $F(ab')_2$ fragment of monoclonal antibody PT85, of any spinal cord damage outcome other than the establishment of partial integration and survival of the porcine xenographic transplant, and partial establishment of synaptic connections, as determined by behavioral testing, or of any neurodegenerative disorder other than the neuropathology of SOD mice, and amyotrophic lateral sclerosis in humans, the unpredictable state of the art with respect to animal models for spinal cord injury and degeneration, antigen/antibody interactions, and transplantation treatment outcomes of spinal cord injury and degeneration, and the breadth of the claims to any and all xenographic subjects, any and all types of spinal cord damage or injury, any and all antigens, any and all cell surface antigen alterations, any and all treatments, any and all molecules, and any and all neurodegenerative disorders, it would have required undue experimentation for one skilled in the art to make and/or use the invention as broadly claimed.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 26-30 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The claims are indefinite in their recitation of "...which is capable of stimulating an immune response...". It is unclear what subject is being modified by this phrase. Is the "molecule" capable of stimulating an immune response, or is the "antigen on the cell surface" capable of stimulating an immune response? In the absence of clarity, the metes and bounds of the claimed invention cannot be determined.

***Claim Rejections - 35 USC § 102***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> > (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

Claims 1, 2, 5-7, 13-16, 18, 19, 22-24, and 31-38 are rejected under 35 U.S.C. 102(e) as being anticipated by Gage et al. (1998). The claims are drawn to a composition for transplantation into a xenographic subject comprising an isolated spinal cord cell selected from the group consisting of an oligodendrocyte, an astrocyte, and a neuron, isolated from an embryonic

pig, and further comprising at least one of the agents or factors selected from the group consisting of neurotrophic factors and anti-inflammatory agents, such that treatment of spinal cord damage is obtained upon transplantation of said composition into the subject. The claims are further drawn to a method of treating a xenographic subject having spinal cord damage by administering to the subject, said composition. Gage et al. teach the composition and method of transplantation of embryonic neuronal cells and glial cells (including astrocytes and oligodendrocytes), as both a homogenous population of cells, or as a mixture, into the spinal cord of a mammalian (including human) subject, to facilitate reconnection or ameliorative interactions of injured and damaged neurons (including those resulting from a neurodegenerative disorder such as amyotrophic lateral sclerosis) in the spinal cord (ie. to treat spinal cord damage.) See column 7, lines 15-20; column 13, lines 34, and 39-46, claims 3, 19, 23, and 25. Furthermore, the composition of Gage et al. further comprises growth factors (ie. neurotrophic factors), and a therapeutic agent (ie. methylprednisolone) for treating disease or damage to the central nervous system. See column 23, lines 1-4 and claims 18 and 19. Therefore, the method and composition of Gage et al. meet the limitations of the claimed invention of the instant application.

### *Claim Rejections - 35 USC § 103*

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are

> such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 3, 4, 8-12, 17, 20, 21, and 25-30 are rejected under 35 U.S.C. 103(a) as being unpatentable over Fraser et al. (1996), further in view of Gage et al. (1998).

The claims are drawn to a composition for transplantation into a rat or a mouse to treat spinal cord damage selected from the group consisting of partial spinal cord transection in said rat and spinal cord degeneration associated with SOD mice, comprising an isolated spinal cord cell obtained from a pig, such that partial integration and survival of the porcine xenographic transplant occurs, and partial synaptic connections are established as determined by behavioral testing; wherein the spinal cord cell is obtained from an embryonic pig between about 20 to 30 days gestation; wherein, prior to introduction into the recipient mouse, the cell is contacted with an anti-MHC class I F(ab')2 fragment of monoclonal antibody PT85, but does not activate complement or induce cell lysis; wherein the composition further comprises at least one agent or factor selected from the group consisting of brain-derived neurotrophic factor, ciliary neurotrophic factor, platelet-derived growth factor, neural growth factor, neurotrophin-3, neurotrophin 4/5, basic fibroblast growth factor, and methylprednisolone; and wherein the cell is obtained from a pig predetermined to be free from at least one organism selected from the groups consisting of zoonotic, cross-placental and neurotropic organisms; and a method of treatment of partial spinal cord transection in rats and spinal cord degeneration associated with SOD (expresses a human Cu/Zn superoxide dismutase mutation) mice comprising administering said

composition to said rat or mouse, such that integration and survival of the porcine xenographic transplant occurs, and synaptic connections are established as determined by behavioral testing; and a method of treatment of spinal cord degeneration comprising amyotrophic lateral sclerosis in humans, comprising administering said composition to said human, such that integration and survival of the porcine xenographic transplant occurs, and synaptic connections are established as determined by behavioral testing.

Fraser et al. teach a composition for transplantation into a xenogeneic subject to treat neurodegeneration in the brain, comprising an isolated cortical cell, mesencephalic cell or striatal cell, obtained from a pig, such that partial integration and survival of the porcine xenographic transplant occurs, and partial synaptic connections are established as determined by behavioral testing; wherein the cortical cell, mesencephalic cell or striatal cell is obtained from an embryonic pig between about 20 to 30 days gestation; wherein, prior to introduction into the recipient mouse, the cell is contacted with an anti-MHC class I F(ab')2 fragment of monoclonal antibody PT85, but does not activate complement or induce cell lysis; wherein the composition further comprises at least one agent or factor selected from the group consisting of brain-derived neurotrophic factor, ciliary neurotrophic factor, platelet-derived growth factor, neural growth factor, neurotrophin-3, neurotrophin 4/5, basic fibroblast growth factor, and methylprednisolone; and wherein the cell is obtained from a pig predetermined to be free from at least one organism selected from the groups consisting of zoonotic, cross-placental and neurotropic organisms; and a method of treatment of neurodegeneration in the brain of a xenogeneic subject by administering to

said subject said composition, such that integration and survival of the porcine xenographic transplant occurs, and synaptic connections are established as determined by behavioral testing. See entire document, especially the claims. Fraser et al., however, fails to teach the use of porcine spinal cord cells to treat spinal cord injury or degeneration in their disclosed composition or method of treatment. Gage et al. do teach the composition and method of treatment of grafting embryonic mammalian donor spinal cord cells into a mammalian subject to facilitate reconnection or ameliorative interactions of injured and damaged neurons in the spinal cord. See entire document, especially claims 3, 23, and 25. While Gage et al. teach a method of treating the donor cells so as to minimize or reduce graft rejection, the authors do not specifically teach contacting the transplant cell with an anti-MHC class I F(ab')2 fragment of monoclonal antibody PT85, that does not activate complement or induce cell lysis. Furthermore, while the claims of Gage et al. read on the harvesting cells from pig embryos, no specific time frame for days gestation is given in order to assure optimal cell harvesting. Furthermore Gage et al. fails to teach obtaining transplant cells from pathogen-free pigs. However, at the time the invention was made, it would have been obvious to one of ordinary skill in the art that pathogen-free donors are an advantage when avoiding infecting the recipient with a pathogen during the transplantation process.

Motivation to combine the references and use spinal cord cells in the composition and method of Fraser et al. to treat spinal cord injuries is taught by Gage et al. who teach "[t]he importance of target-donor matching: neurons survive better when they are grafted to a site which

they would normally innervate." See column 2, lines 28-30. Further motivation to treat the donor cells so as to minimize or reduce graft rejection is taught in claim 1 of Gage et al.

Therefore, it would have been *prima facie* obvious at the time the invention was made, for one of ordinary skill in the art to combine the above references and combine the composition and methods, as taught by Fraser et al. with the use of porcine spinal cord cells, as taught by Gage et al., to arrive at the composition for transplantation into a rat or a mouse to treat spinal cord damage selected from the group consisting of partial spinal cord transection in said rat and spinal cord degeneration associated with SOD mice, comprising an isolated spinal cord cell obtained from a pig, such that partial integration and survival of the porcine xenographic transplant occurs, and partial synaptic connections are established as determined by behavioral testing; wherein, prior to introduction into the recipient mouse, the cell is contacted with an anti-MHC class I F(ab')2 fragment of monoclonal antibody PT85, but does not activate complement or induce cell lysis; wherein the composition further comprises at least one agent or factor selected from the group consisting of brain-derived neurotrophic factor, ciliary neurotrophic factor, platelet-derived growth factor, neural growth factor, neurotrophin-3, neurotrophin 4/5, basic fibroblast growth factor, and methylprednisolone; and wherein the cell is obtained from a pig predetermined to be free from at least one organism selected from the groups consisting of zoonotic, cross-placental and neurotropic organisms; and a method of treatment of partial spinal cord transection in rats and spinal cord degeneration associated with SOD (expresses a human Cu/Zn superoxide dismutase mutation) mice comprising administering said composition to said rat or mouse, such

that integration and survival of the porcine xenographic transplant occurs, and synaptic connections are established as determined by behavioral testing; and a method of treatment of partial spinal cord transection and spinal cord degeneration comprising amyotrophic lateral sclerosis in humans, comprising administering said composition to said human, such that integration and survival of the porcine xenographic transplant occurs, and synaptic connections are established as determined by behavioral testing of the claimed invention. Furthermore, one of ordinary skill in the art would have had a reasonable expectation of success, and used porcine spinal cord cell in the composition and methods of Fraser et al. for the benefit of performing and enhanced modification of improving transplant survivability in treating spinal cord injury and neurodegeneration in xenogeneic subjects.

## *Conclusion*

No claim is allowed, for the reasons outlined above.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kris Pelham Mayo whose telephone number is (703) 306-5877. The examiner can normally be reached on Monday-Friday from 8:00 a.m. to 4:30 p.m. (Eastern Time).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jasemine Chambers, can be reached at (703)308-2035. The FAX phone number for group 1600 is (703)308-4242.

An inquiry of a general nature or relating to the status of the application should be directed to the group receptionist whose telephone number is (703)308-0196.

Kris Pelham Mayo, D.V.M.
Patent Examiner
Art Unit 1633
December 6, 1999

DEBORAH J. CLARK
PATENT EXAMINER